UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,039	06/23/2005	Tetsuro Kokubo	4439-4023	8665

27123 7590 04/24/2006

MORGAN & FINNEGAN, L.L.P.
3 WORLD FINANCIAL CENTER
NEW YORK, NY 10281-2101

EXAMINER	
LIETO, LOUIS D	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/501,039	KOKUBO ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) 7-10 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☒ Claim(s) *7-10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10 are pending and under consideration

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

Claims 7-10 are objected to under 37 CFR 1.75(c) as being in improper form because multiple dependent claims 7-10 depend from multiple dependent claims 6-9. See MPEP § 608.01(n). Accordingly, claims 7-10 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of monitoring expression of a gene encoding a protein that varies a NMR signal and can be quantified by NMR, without the requirement to add an exogenous substrate, does not reasonably provide enablement for a method of monitoring expression of monitoring expression of a chosen gene, wherein the accumulation of any

molecule that varies a NMR signal and can be quantified by NMR is measured. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims have been interpreted to be drawn to measuring the expression of any gene, *in vitro* or *in vivo*, by accumulation of any molecule, such as any polyphosphate or any type of cytochrome, that varies an NMR signal and can be quantified by NMR, without the requirement of adding an exogenous substrate. Wherein the monitoring may be practiced using non-destructive NMR quantification. The claims broadly encompass any method of monitoring any expressed protein using NMR, as long as an exogenous substrate is not added.

The specification indicates that the invention is directed towards monitoring transcription activity of a promoter, *in vivo*, through non-destructive NMR quantification. Wherein the promoter is operably linked to a polyphosphate reporter gene. Further, it is noted that claims encompass destructive NMR quantification as well. It was known in the art at the time of filing that *in vivo*, non-destructive monitoring of gene expression was possible using a similar system incorporating a promoter linked to a luciferase gene {Contag et al. (1997) Phtochem. Photbiol. 66:523-31; abstract}. Further, The art teaches that numerous molecules can monitored using NMR, without an exogenous substrate. These molecules include transferrin, cytochrome-c, phosphocreatine and polyphosphate {Sharfstein et al. (1994) Ann NY Acad. Sci. 745:77-91, pg. 80; Materials and Methods; Gropman A. (2001) Curr. Neurol. Neurosci. Rep. 1:185-94, pg. 189; Koretsky et al. (1996) Proceedings of the 4th Int. Soc. Magnetic. Resonance Med. Pg. 69}. However, the art teaches that it is difficult to monitor the expression of genes, such as

phosphocreatine in tissues with high background expression. The same problems are likely to affect any chosen molecule in a method of *in vivo* monitoring.

It is noted that neither the specification nor the art of record at the time of filing teach how to monitor the expression of a gene, by NMR, by monitoring any molecule that accumulates in a manner independent from the expression of the chosen gene. The claims broadly encompass such a method. However, the skilled practitioner would be unable to predict how to practice the claimed method without determining for himself what the nexus or link was between the chosen gene and the molecule that was accumulated. Such determination would be comprise undue and extensive experimentation. Therefore the skilled practitioner would be unable to practice the claimed method in a manner commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Claim 1 is a method of monitoring gene expression, however there is no method step linking the gene to be monitored and the accumulation of the NMR varying molecule. It is unclear how the molecule to quantified is related to the gene being monitored. Claims 2-6 depend from claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1- 4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by {Sharfstein et al. (1994) Ann NY Acad. Sci. 745:77-91}.

Sharfstein et al. provides guidance on monitoring polyphosphate metabolism in E. *coli* by non-destructive quantification of polyphosphate by NMR (pg. 80; Materials and Methods). Sharfstein et al. monitored the changes of intracellular polyphosphates during shifts from phosphate-starvation to phosphate rich conditions (pg. 80). Sharfstein et al. teaches that the levels of phosphate present in the E. *coli* culture conditions effect the gene expression and/or degradation of polyphosphate kinase (ppk) and polyphosphatase (ppx) (pg. 78). Wherein the ppx is in-frame and downstream of the ppk gene (figure, 78). Thus by quantifying the levels of polyphosphate in E. *coli* by NMR, under different phosphate conditions Sharfstein et al. is inherently monitoring the expression of the ppx and ppk genes. Thus, by teaching all the limitations of the claims as written, Sharfstein et al. anticipates the instant invention as claimed.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by {van Voorthuysen et al. (2000) J. Biotech. 77:65-80}.

van Voorthuysen et al. provides guidance on measuring polyphosphate levels metabolism in potato plant leaves by quantification of polyphosphate via NMR (Abstract). van Voorthuysen et al. teaches the transformation of potato plants with a ppk gene fused to the leader sequence of a feeredoxin oxirductase gene (FNR) under the control of a leaf specific St-LS1 promoter (Abstract; pg. 67, materials and methods). Further, van Voorthuysen et al. teaches that polyphosphate levels were measured in leaf tissue from extracts made from leaf biopsies by NMR (pg. 67-68, materials and methods). Thus, by teaching all the limitations of the claims as written, van Voorthuysen et al. anticipates the instant invention as claimed.

Claims 1,2 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by {Walter et al. (2000) PNAS 97:5151-5155}.

Walter et al. provides guidance on quantifying phosphoarginine levels in mouse skeletal muscle by non-destructive quantification of phosphate by NMR (Abstract). Walter et al. teaches the transformation of mouse skeletal muscle *in situ* with a recombinant adenovirus expressing phosphoarginine (Abstract; pgs. 5151-5152, Methods). Further, Walter et al. teaches that two weeks after injection of the Ad vector a unique 31P-MRS resonance was observed within injected limbs, which was not present in uninjected control limbs (Abstract; pg. 5153, Figures 2-4). Thus, by teaching all the limitations of the claims as written, Walter et al. anticipates the instant invention as claimed.

Claims 1,5 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by {Gropman A. (2001) Curr. Neurol. Neurosci. Rep. 1:185-94}.

Gropman A. provides guidance on non-invasive screening evaluation of childhood mitochondrial diseases (pg. 189). Gropman A. teaches that childhood mitochondrial diseases include diseases such as Leigh Syndrome, which is caused by defective expression of cytochrome-c (pg. 187). Finally, Gropman A. provides guidance on the use of NMR to analyze CSF lactate and 31P levels which can be used to diagnose a mitochondrial disorder due to defective expression of a cytochrome (pg. 190). Thus, by teaching all the limitations of the claims as written, Gropman A. anticipates the instant invention as claimed.

Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by {Ozawa et al. (2001) Biosci, Biotech, Biochem 65:185-189}.

Ozawa et al. provides guidance on the expression of multiheme cytochrome C, its isolation and quantification with NMR (Abstract; pg. 187, Fig. 3). Thus, by teaching all the limitations of the claims as written, Ozawa et al. anticipates the instant invention as claimed.

Claims 1 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by {Koretsky et al. (1996) Proceedings of the 4th Int. Soc. Magnetic. Resonance Med. Pg. 69}.

Koretsky et al. provides guidance on quantifying transferring levels in mouse tumors expressing the human transferrin receptor. (Introduction). Koretsky et al. teaches the transformation of mouse ear fibroblasts with a recombinant adenovirus and a DNA construct encoding human transferrin (Material and Methods). Further, Koretsky et al. teaches that the mice were injected with the transformed cells, which formed tumors that were observed in the living mice via MRI was observed within injected limbs (Material and Methods). The expression

levels of the human transferring receptor were quantified in the tumor, due to transferrin's ability to bind endogenous iron, and compared to tumors in fibroblast tumors in the mice, which did not express human transferring. Thus, by teaching all the limitations of the claims as written, Koretsky et al. anticipates the instant invention as claimed.

No claims allowed

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Dr. Louis D. Lieto
Patent Examiner
Art Unit 1632